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Synthesis of New 3-(Alkylsulfanyl)pyrano[3,4-*c*]-[1,2,4]triazolo[4,3-*a*]pyridines

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Abstract—A new method has been developed for the synthesis of 8-hydrazinylpyrano[3,4-*c*]pyridines via pyridine ring rearrangement. New 3-(alkylsulfanyl)pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridines have been obtained.

Keywords: 8-hydrazinylpyrano[3,4-*c*]pyridines, rearrangement, triazolo[4,3-*a*]pyridines, pyrano[3,4-*c*][1,2,4]-triazolo[4,3-*a*]pyridines, S-alkyl derivatives.

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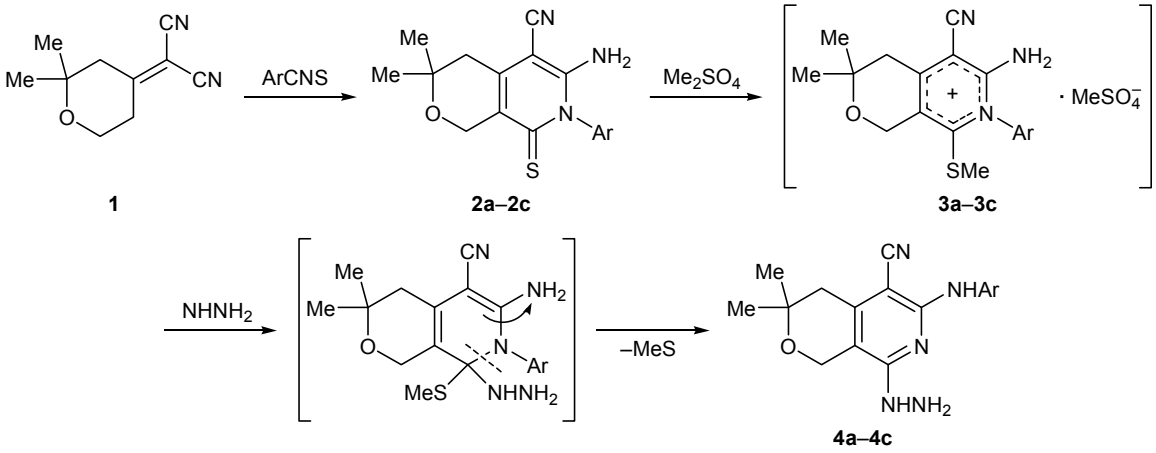
Synthetic pyridine derivatives are biologically active compounds, and fused pyridine-containing heterocyclic systems are considerably more interesting than the corresponding monocyclic pyridines. For example, triazolopyridine derivatives exhibit antimicrobial and antitumor activity [1–3], and 2-{3-[4-(3-chlorophenyl)-piperazin-1-yl]propyl}[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one (trazodone) is known as an antidepressant medication [4]. On the other hand, fused tricyclic triazolopyridine derivatives have been poorly studied, and there are a few published data on the synthesis and biological activity of triazoloisoquinolines and triazolopyranopyridines [5–8].

In continuation of our studies of the synthesis and properties of fused pyridine derivatives, herein we report a new method for the preparation of tricyclic 3-(alkylsulfanyl)pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]-pyridines **6a**–**6t**. The starting material was 2-(2,2-dimethyltetrahydro-4*H*-pyran-4-ylidene)malononitrile (**1**) [9] which reacted with aryl isothiocyanates to give 6-aminopyrano[3,4-*c*]pyridine-8-thiones **2a**–**2c**. The latter were converted to pyridinium salts **3a**–**3c** by the action of dimethyl sulfate, and salts **3a**–**3c** were treated without isolation with 80% hydrazine hydrate. The reaction was accompanied by rearrangement of the pyridine ring according to a mechanism identical to that proposed in [10]. We thus obtained 8-hydrazinylpyrano[3,4-*c*]pyridines **4a**–**4c** in high yields. We previously reported [11] a procedure for the synthesis of **4a** and **4b** by directly reacting compounds **2a** and **2b** with hydrazine hydrate, but the yields were lower (Scheme 1). The reaction of **4a**–**4c** with carbon disulfide in pyridine gave 3-sulfanylidenepyrano[3,4-*c*]-[1,2,4]triazolo-[4,3-*a*]pyridines **5a**–**5c** which were alkylated with various alkyl halides to afford 70–75% of 3-(alkylsulfanyl)pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]-pyridines **6a**–**6t** (Scheme 2).

The IR spectra of **6a**–**6t** contained NH stretching bands in the region 3318–3328 cm^{-1} and CN stretching bands at 2208–2212 cm^{-1}. In the ^1H NMR spectra of **6a**–**6t**, protons of the SMe or SCH_2 group resonated at δ 2.65 or 3.98–4.82 ppm, respectively, and the SCH_3 and SCH_2 carbon signals in the ^{13}C NMR spectra of **6a** and **6n** were located at δ_C 15.2 and 36.4 ppm, respectively. The NMR data confirmed the formation of *S*-substituted products [12]. The observed regioselectivity may be rationalized by the high polarizability of the sulfur atom compared to nitrogen [13].

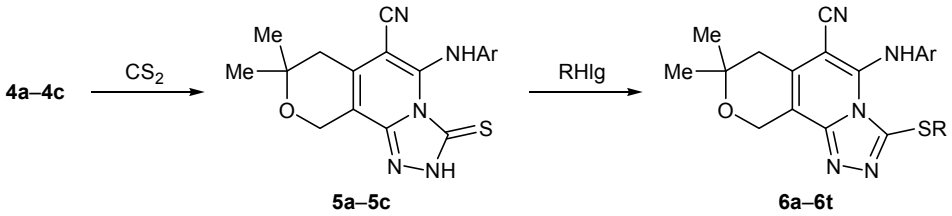
The anticonvulsant activity of compounds **6a**–**6t** was assayed in 18–24-g male and female white mice (160 animals) using ethosuximide as reference drug. The anticonvulsant and potential anxiolytic activities were evaluated by the prevention of clonic twitches and clonic component of pentylenetetrazole-induced seizures (90 mg/kg subcutaneously) [14]. The central myorelaxant effect and motor coordination disorder were studied by the rotarod method [14]. The tested compounds were administered intraperitoneally as sus-

Scheme 1.



2–**4**, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 2-MeC_6H_4 (**c**).

Scheme 2.



5, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 2-MeC_6H_4 (**c**); **6**, Ar = Ph, R = Me (**a**), Pr (**b**), $HOC(O)CH_2$ (**c**), R = $Me_2N(CH_2)_2$ (**d**), 4-$FC_6H_4CH_2$ (**e**), 4-$ClC_6H_4COCH_2$ (**f**), R = 2-oxo-2-(pyrrolidin-1-yl)ethyl (**g**), R = 3-$MeOC_6H_4NHC(O)CH_2$ (**h**), 2,4-$(MeO)_2C_6H_3NHC(O)CH_2$ (6**i**); Ar = 4-MeC_6H_4, R = $Me_2CH(CH_2)_2$ (**j**), $MeOC(O)CH_2$ (**k**), 4-$FC_6H_4CH_2$ (**l**), 2-$ClC_6H_4CH_2$ (**m**), 1*H*-benzimidazol-2-ylmethyl (**n**), 3-$O_2NC_6H_4C(O)CH_2$ (**o**), $PhNHC(O)CH_2$ (**p**), $PhCH_2NHC(O)CH_2$ (**q**), 2-oxo-2-(1,3-thiazol-2-ylamino)ethyl (**r**), 2-$MeOC_6H_4NHC(O)CH_2$ (**s**); Ar = 2-MeC_6H_4, R = 2-oxo-2-(pyrrolidin-1-yl)ethyl (**t**).

pensions in twin-80 at a dose of 50 mg/kg 45 min before pentylenetetrazole injection; ethosuximide was administered at a dose of 150 mg/kg. Compounds **6e**–**6i**, **6l**, **6m**, **6q**, and **6s** prevented pentylenetetrazole-induced seizures in 20–40% of animals. Furthermore, the examined compounds and ethosuximide at the given doses did not cause myorelaxant effect.

Thus, we have proposed methods for the synthesis of 8-hydrazinylpyrano[3,4-*c*]pyridines and alkylsulfanyl derivatives of a new heterocyclic system, pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridines, on the basis of pyridine ring rearrangement.

EXPERIMENTAL

The IR spectra were recorded in mineral oil on a Nicolet Avatar 330 FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 Vx spectrometer at 300 and 75.462 MHz, respectively, using tetramethylsilane as internal standard. If necessary, DEPT, NOESY (mixing time 1 s), and HMQC techniques were applied to assign signals in the NMR spectra. The melting points were measured on a Boetius micro hot stage. Analytical thin-layer chromatography was performed on Silufol UV-254 plates using pyridine–diethyl ether (1:3, **2c**), pyridine–ethanol (1:3, **4c**), pyridine–ethyl acetate (2:1, **5c**), or butan-1-ol–acetic acid–water (4:2:5, **6a**–**6t**) as eluent.

Compounds **2a**, **2b**, **5a**, and **5b** were synthesized according to the procedures described in [10, 11].

6-Amino-3,3-dimethyl-7-(2-methylphenyl)-8-sulfanylidene-3,4,7,8-tetrahydro-1*H*-pyrano[3,4-*c*]-pyridine-5-carbonitrile (2c). Triethylamine, 1 mL, was added dropwise with stirring to a solution of 1.76 g 10 mmol of 2-(2,2-dimethyltetrahydro-4*H*-pyran-4-ylidene)malononitrile (**1**) and 1.49 g 10 mmol of 1-isothiocyanato-2-methylbenzene in 2 mL of dimethylformamide. The mixture was heated for 1 h at 50°C and cooled to room temperature, and 4 mL of methanol was added. The precipitate was filtered off,

washed with water, and recrystallized from nitromethane. Yield 2.6 g (80%), mp 296–297°C. IR spectrum, ν, cm^{-1}: 3315, 3208 (NH_2), 2208 (CN), 1245 (C=S). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 s (6H, CH_3), 2.06 s (3H, CH_3), 2.55 s (2H, 4-H), 4.36 d and 4.40 d (1H each, 1-H, J = 16.6 Hz), 6.48 br.s (2H, NH_2), 7.02–7.09 m (1H, H_{arom}), 7.36–7.45 m (3H, H_{arom}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 16.6 (CH_3), 25.8 (CH_3), 26.1 (CH_3), 37.4 (CH_2), 61.6 and 68.7 (OCH_2), 78.4, 115.0, 122.7, 127.6 (CH), 127.7 (CH), 129.2 (CH), 131.5 (CH), 135.0, 136.4, 141.6, 153.4, 177.1 (CS). Found, %: C 66.54; H 5.75; N 12.79; S 9.76. $C_{18}H_{19}N_3OS$. Calculated, %: C 66.43; H 5.88; N 12.91; S 9.85.

Compounds 4a–4c (*general procedure*). A mixture of 10 mmol of compound **2a**–**2c**, 15 mmol of dimethyl sulfate, and 20 mL of toluene was refluxed for 10–15 min. The mixture was cooled, the solvent was removed by decanting, the oily residue (compound **3a**–**3c**) was dissolved in 30 mL of methanol, and 20 mL of 80% hydrazine hydrate was added. The mixture was refluxed for 30 min and cooled to room temperature, and the precipitate was filtered off, washed with water, dried, and recrystallized from dioxane.

The spectral data of **4a** and **4b** were reported previously [11].

6-Anilino-8-hydrazinyl-3,3-dimethyl-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (4a). Yield 2.72 g (88%), mp 230–231°C.

8-Hydrazino-3,3-dimethyl-6-(4-methylanilino)-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (4b). Yield 2.62 g (81%), mp 228–229°C.

8-Hydrazinyl-3,3-dimethyl-6-(2-methylanilino)-3,4-dihydro-1*H*-pyrano[3,4-*c*]pyridine-5-carbonitrile (4c). Yield 2.75 g (85%), mp 240–242°C. IR spectrum, ν, cm^{-1}: 3380, 3318, 3210 (NH, NH_2), 2203 (CN). ^1H (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.26 s (6H, CH_3), 2.30 s (3H, CH_3), 2.55 s (2H, 4-H), 3.55 br (2H, NH_2), 4.31 s (2H, 2-H), 6.93–7.00 m (1H, H_{arom}), 7.10–7.17 m (2H, H_{arom}), 7.34 s (1H, 6-NH), 7.71–7.76 m (1H, H_{arom}), 7.87 br (1H, 8-NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 17.7 (CH_3), 25.9 (2C, CH_3), 37.5 (CH_2), 57.8, 68.9 (OCH_2), 78.5, 103.4, 116.8, 123.2 (CH), 123.6 (CH), 125.5 (CH), 129.6 (CH), 130.0, 137.7, 144.0, 154.9, 155.8. Found, %: C 66.76; H 6.59; N 21.53. $C_{18}H_{21}N_5O$. Calculated, %: C 66.85; H 6.55; N 21.66.

8,8-Dimethyl-5-(2-methylanilino)-3-sulfanylidene-2,3,7,10-tetrahydro-8*H*-pyrano[3,4-*c*][1,2,4]-triazolo[4,3-*a*]pyridine-6-carbonitrile (5c). A mixture of 1.62 g (5 mmol) of compound **4c**, 10 mL of carbon disulfide, and 20 mL of pyridine was refluxed for 15 h. The solvent was removed under reduced pressure, and the crude product was dissolved in a solution of 0.28 g (5 mmol) of potassium hydroxide in a mixture of 10 mL of water and 30 mL of ethanol. The solution was acidified with 10% aqueous HCl, and the precipitate was filtered off, washed with water, and recrystallized from ethanol–chloroform, 1:1. Yield 1.54 g (84%), mp 233–235°C. IR spectrum, ν, cm^{-1}: 3365 (NH), 3230 (NH), 2207 (CN), 1225 (C=S). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.28 s (6H, CH_3), 2.38 t (2H, 7-H, J = 1.7 Hz), 2.40 s (3H, CH_3), 4.53 t (2H, 10-H, J = 1.7 Hz), 7.21–7.30 m (4H, H_{arom}), 12.66 s (1H, NH), 14.69 br.s (1H, NH). Found, %: C 62.52; H 5.27; N 19.27; S 8.68. $C_{19}H_{19}N_5OS$. Calculated, %: C 62.44; H 5.24; N 19.16; S 8.77.

Compounds 6a–6t (*general procedure*). Compound **5a**–**5c** (2 mmol) was added to a solution of 112 mg (2 mmol) of potassium hydroxide in a mixture of 2 mL of water and 12 mL of ethanol. When the mixture became homogeneous, 2 mmol of the corresponding alkyl halide was added with cooling. The mixture was stirred for 12 h at room temperature, and the precipitate was filtered off, washed with water, and recrystallized from ethanol–chloroform (2:1).

5-Anilino-8,8-dimethyl-3-(methylsulfanyl)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6a). Yield 0.54 g (74%), mp 186–187°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2210 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 s (6H, CH_3), 2.64 s (2H, 7-H), 2.65 s (3H, SCH_3), 4.86 s (2H, 10-H), 6.74–6.80 m (2H, H_{arom}), 6.90 t.t (1H, H_{arom}, J = 7.4, 0.9 Hz), 7.18–7.26 m (2H, H_{arom}), 9.04 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ_C, ppm: 15.2 (SCH_3), 25.9 (2C, CH_3), 36.3 (CH_2), 57.8, 69.8 (OCH_2), 113.1, 115.8 (2C, CH), 118.1, 120.8, 128.7 (3C, CH), 130.5, 140.7, 142.9, 143.5, 148.4. Found, %: C 62.53; H 5.19; N 19.23; S 8.69. $C_{19}H_{19}N_5OS$. Calculated, %: C 62.44; H 5.24; N 19.16; S 8.77.

5-Anilino-8,8-dimethyl-3-(propylsulfanyl)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6b). Yield 0.57 g (72%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 3318 (NH), 2210 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.04 t (3H, CH_3, J = 7.4 Hz), 1.30 s (6H, CH_3), 1.93 q (2H, CH_2CH_3, J = 7.4 Hz), 2.44 t (2H, 7-H, J = 1.8 Hz), 4.17–4.23 m (2H, SCH_2), 4.54 t (2H, 10-H,

J = 1.8 Hz), 7.26–7.33 m (3H, H_{arom}), 7.39–7.46 m (2H, H_{arom}), 12.72 s (1H, NH). Found, %: C 64.03; H 5.92; N 17.71; S 8.22. $C_{21}H_{23}N_5OS$. Calculated, %: C 64.10; H 5.89; N 17.80; S 8.15.

[(5-Anilino-6-cyano-8,8-dimethyl-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-sulfanyl]acetic acid (6c). Yield 0.57 g (70%), mp 164–166°C. IR spectrum, ν, cm^{-1}: 3320–3400 (NH, OH), 2208 (CN), 1705 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 s (6H, CH_3), 2.62 s (2H, 7-H), 3.10 br.s (1H, OH), 3.98 s (2H, SCH_2), 4.87 s (2H, 10-H), 6.88–6.99 m (3H, H_{arom}), 7.21–7.29 m (2H, H_{arom}), 9.35 br.s (1H, NH). Found, %: C 58.73; H 4.65; N 17.18; S 7.77. $C_{20}H_{19}N_5O_3S$. Calculated, %: C 58.67; H 4.68; N 17.10; S 7.83.

5-Anilino-3-{[2-(dimethylamino)ethyl]sulfanyl}-8,8-dimethyl-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]-triazolo[4,3-*a*]pyridine-6-carbonitrile (6d). Yield 0.61 g (72%), mp 158–159°C. IR spectrum, ν, cm^{-1}: 3327 (NH), 2212 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 s (6H, CH_3), 2.29 s [6H, $N(CH_3)_2$], 2.44 s (2H, 7-H), 2.79 t (2H, NCH_2, *J* = 6.6 Hz), 4.32 t (2H, SCH_2, *J* = 6.6 Hz), 4.55 s (2H, 10-H), 7.27–7.32 m (3H, H_{arom}), 7.37–7.46 m (2H, H_{arom}), 12.69 s (1H, NH). Found, %: C 62.58; H 6.16; N 19.95; S 7.49. $C_{22}H_{26}N_6OS$. Calculated, %: C 62.53; H 6.20; N 19.89; S 7.59.

5-Anilino-3-[(4-chlorobenzyl)sulfanyl]-8,8-dimethyl-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6e). Yield 0.64 g (70%), mp 170–171°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2208 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 s (6H, CH_3), 2.62 s (2H, 7-H), 4.39 s (2H, SCH_2), 4.87 s (2H, 10-H), 6.74–6.79 m (2H, H_{arom}), 6.88–6.96 m (3H, H_{arom}), 7.18–7.33 m (4H, H_{arom}), 9.07 s (1H, NH). Found, %: C 65.42; H 4.79; N 15.31; S 7.05. $C_{25}H_{22}FN_5OS$. Calculated, %: C 65.34; H 4.83; N 15.24; S 6.98.

5-Anilino-3-{[2-(4-chlorophenyl)-2-oxoethyl]-sulfanyl}-8,8-dimethyl-7,10-dihydro-8*H*-pyrano-[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6f). Yield 0.71 g (71%), mp 213–214°C. IR spectrum, ν, cm^{-1}: 3322 (NH), 2210 (CN), 1685 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 s (6H, CH_3), 2.64 s (2H, 7-H), 4.82 s (4H, SCH_2, 10-H), 6.88–6.99 m (3H, H_{arom}), 7.22–7.28 m (2H, H_{arom}), 7.45–7.51 m (2H, H_{arom}), 7.98–8.04 m (2H, H_{arom}), 9.33 br.s (1H, NH). Found, %: C 61.85; H 4.46; N 13.81; S 6.43. $C_{26}H_{22}ClN_5O_2S$. Calculated, %: C 61.96; H 4.40; N 13.90; S 6.36.

5-Anilino-8,8-dimethyl-3-{[2-oxo-2-(pyrrolidin-1-yl)ethyl]sulfanyl}-7,10-dihydro-8*H*-pyrano[3,4-*c*]-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6g). Yield 0.65 g (70%), mp 228–229°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2212 (CN), 1665 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 s (6H, CH_3), 1.80–1.90 m (2H, CH_2), 1.92–2.02 m (2H, CH_2), 2.63 s (2H, 7-H), 3.38 t (2H, NCH_2, *J* = 6.8 Hz), 3.51 t (2H, NCH_2, *J* = 6.7 Hz), 4.14 s (2H, SCH_2), 4.85 s (2H, 10-H), 6.98–7.05 m (3H, H_{arom}), 7.25–7.34 m (2H, H_{arom}), 10.28 br.s (1H, NH). Found, %: C 62.39; H 5.63; N 18.25; S 6.86. $C_{24}H_{26}N_6O_2S$. Calculated, %: C 62.32; H 5.67; N 18.17; S 6.93.

2-[(5-Anilino-6-cyano-8,8-dimethyl-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridin-3-yl)sulfanyl]-*N*-(3-methoxyphenyl)acetamide (6h). Yield 0.74 g (72%), mp 227–228°C. IR spectrum, ν, cm^{-1}: 3370, 3327 (NH), 2210 (CN), 1668 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.33 s (6H, CH_3), 2.63 s (2H, 7-H), 3.75 s (3H, OCH_3), 4.16 s (2H, SCH_2), 4.83 s (2H, 10-H), 6.54 d.d.d (1H, H_{arom}, *J* = 8.0, 2.5, 1.1 Hz), 6.94–7.14 m (5H, H_{arom}), 7.22–7.31 m (3H, H_{arom}), 9.55 s (1H, NH), 10.15 s (1H, NH). Found, %: C 63.11; H 5.06; N 16.24; S 6.15. $C_{27}H_{26}N_6O_3S$. Calculated, %: C 63.02; H 5.09; N 16.33; S 6.23.

2-[(5-Anilino-6-cyano-8,8-dimethyl-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridin-3-yl)sulfanyl]-*N*-(2,4-dimethoxyphenyl)acetamide (6i). Yield 0.76 g (70%), mp 219–220°C. IR spectrum, ν, cm^{-1}: 3374, 3328 (NH), 2212 (CN), 1665 (CO). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.39 s (6H, CH_3), 2.63 s (2H, 7-H), 3.75 s (3H, OCH_3), 3.82 s (3H, OCH_3), 4.13 s (2H, SCH_2), 4.87 s (2H, 10-H), 6.38 d.d (1H, H_{arom}, *J* = 8.8, 2.6 Hz), 6.45 d (1H, H_{arom}, *J* = 2.6 Hz), 6.90–7.01 m (3H, H_{arom}), 7.22–7.29 m (2H, H_{arom}), 7.85 d (1H, H_{arom}, *J* = 8.8 Hz), 9.46 br.s (1H, NH), 9.54 s (1H, NH). Found, %: C 61.81; H 5.13; N 15.51; S 5.82. $C_{28}H_{28}N_6O_4S$. Calculated, %: C 61.75; H 5.18; N 15.43; S 5.89.

8,8-Dimethyl-3-[(3-methylbutyl)sulfanyl]-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*]-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6j). Yield 0.64 g (73%), mp 182–183°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2210 (CN). ^{1}H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.03 d [6H, $CH(CH_3)_2$, *J* = 6.4 Hz], 1.30 s (6H, CH_3), 1.65–1.80 m (3H, CH, SCH_2CH_2,), 2.42 s (5H, 7-H, CH_3), 4.20–4.27 m (2H, SCH_2), 4.53 s (2H, 10-H), 7.15–7.25 m (4H, H_{arom}), 12.61 br.s (1H, NH). Found, %: C 66.27; H 6.68;

N 16.15; S 7.28. $C_{24}H_{29}N_5OS$. Calculated, %: C 66.18; H 6.71; N 16.08; S 7.36.

Methyl ({6-cyano-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo-[4,3-*a*]pyridin-3-yl}sulfanyl)acetate (6k). Yield 0.66 g (75%), mp 143–144°C. IR spectrum, ν, cm^{-1}: 3326 (NH), 2212 (CN), 1709 (CO). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.35 s (6H, CH_3), 2.32 s (3H, CH_3), 2.63 s (2H, 7-H), 3.69 s (3H, OCH_3), 4.03 s (2H, SCH_2), 4.84 s (2H, 10-H), 6.75–6.81 m (2H, H_{arom}), 7.03–7.08 m (2H, H_{arom}), 9.09 s (1H, NH). Found, %: C 60.45; H 5.26; N 16.09; S 7.25. $C_{22}H_{23}N_5O_3S$. Calculated, %: C 60.39; H 5.30; N 16.01; S 7.33.

3-[(4-Fluorobenzyl)sulfanyl]-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*]-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6l). Yield 0.66 g (70%), mp 175–176°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2208 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.32 s (3H, CH_3), 2.61 s (2H, 7-H), 4.39 s (2H, SCH_2), 4.84 s (2H, 10-H), 6.68–6.74 m (2H, H_{arom}), 6.88–6.96 m (2H, H_{arom}), 6.99–7.06 m (2H, H_{arom}), 7.25–7.32 m (2H, H_{arom}), 8.98 br.s (1H, NH). Found, %: C 66.02; H 5.05; N 14.85; S 6.71. $C_{26}H_{24}FN_5OS$. Calculated, %: C 65.94; H 5.11; N 14.79; S 6.77.

3-[(2-Chlorobenzyl)sulfanyl]-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*]-[1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6m). Yield 0.70 g (71%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 3327 (NH), 2210 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.32 s (3H, CH_3), 2.60 s (2H, 7-H), 4.51 s (2H, SCH_2), 4.85 s (2H, 10-H), 6.70–6.76 m (2H, H_{arom}), 7.01–7.05 m (2H, H_{arom}), 7.11–7.25 m (2H, H_{arom}), 7.30–7.40 m (2H, H_{arom}), 9.03 s (1H, NH). Found, %: C 63.66; H 4.97; N 14.21; S 6.63. $C_{26}H_{24}ClN_5OS$. Calculated, %: C 63.73; H 4.94; N 14.29; S 6.54.

3-[(1*H*-Benzimidazol-2-ylmethyl)sulfanyl]-8,8-dimethyl-5-(4-methylanilino)]-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6n). Yield 0.69 g (70%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 3408, 3325 (NH), 2210 (CN). ^1H NMR spectrum (DMSO-d_6–CCl_4, 1:3), δ, ppm: 1.33 s (6H, CH_3), 2.33 s (3H, CH_3), 2.60 s (2H, 7-H), 4.64 s (2H, SCH_2), 4.82 s (2H, 10-H), 6.87–6.93 m (2H, H_{arom}), 7.03–7.14 m (4H, H_{arom}), 7.41–7.47 m (2H, H_{arom}), 10.09 br.s (1H, NH), 12.53 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 20.3 (CH_3), 25.9 (2C, CH_3), 32.5 (CH_2), 36.4 (SCH_2), 57.7, 69.8 (OCH_2), 90.4, 113.1, 114.4, 115.1 (CH), 118.0 (2C, CH), 121.7 (2C, CH), 129.2 (3C, CH), 131.1, 132.2 (2C), 137.7, 138.3, 141.6, 141.9, 148.5, 149.8. Found, %: C 65.37; H 5.12; N 19.72; S 7.53. $C_{27}H_{25}N_7OS$. Calculated, %: C 65.43; H 5.08; N 19.78; S 6.47.

8,8-Dimethyl-5-(4-methylanilino)-3-{[2-(3-nitrophenyl)-2-oxoethyl]sulfanyl}-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6o). Yield 0.74 g (70%), mp 233–235°C. IR spectrum, ν, cm^{-1}: 3328 (NH), 2210 (CN), 1640 (CO), 1540, 1350 (NO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.30 s (3H, CH_3), 2.62 s (2H, 7-H), 4.82 s (2H, SCH_2), 4.92 s (2H, 10-H), 6.79–6.84 m (2H, H_{arom}), 6.99–7.09 m (2H, H_{arom}), 7.79 t (1H, H_{arom}, J = 8.1 Hz), 8.38–8.47 m (2H, H_{arom}), 8.78 t (1H, H_{arom}, J = 1.8 Hz), 9.22 s (1H, NH). Found, %: C 61.43; H 4.55; N 15.97; S 6.13. $C_{27}H_{24}N_6O_4S$. Calculated, %: C 61.35; H 4.58; N 15.90; S 6.07.

2-{[6-Cyano-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo-[4,3-*a*]pyridin-3-yl]sulfanyl}-*N*-phenylacetamide (6p). Yield 0.75 g (75%), mp 235–236°C. IR spectrum, ν, cm^{-1}: 3375, 3320 (NH), 2210 (CN), 1665 (CO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.34 s (3H, CH_3), 2.60 s (2H, 7-H), 4.15 s (2H, SCH_2), 4.82 s (2H, 10-H), 6.89–7.03 m (3H, H_{arom}), 7.06–7.11 m (2H, H_{arom}), 7.19–7.26 m (2H, H_{arom}), 7.51–7.56 m (2H, H_{arom}), 9.56 br.s (1H, NH), 10.17 br.s (1H, NH). Found, %: C 64.98; H 5.31; N 16.95; S 6.51. $C_{27}H_{26}N_6O_2S$. Calculated, %: C 65.04; H 5.26; N 16.86; S 6.43.

***N*-Benzyl-2-{[6-cyano-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridin-3-yl]sulfanyl}acetamide (6q).** Yield 0.75 g (73%), mp 222–223°C. IR spectrum, ν, cm^{-1}: 3367, 3325 (NH), 2212 (CN), 1670 (CO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.33 s (3H, CH_3), 2.61 s (2H, 7-H), 4.20 s (2H, SCH_2), 4.83 s (2H, 10-H), 6.84–6.89 m (2H, H_{arom}), 7.04–7.09 m (2H, H_{arom}), 6.99 d (1H, SCH, J = 3.5 Hz), 7.37 d (1H, NCH, J = 3.5 Hz), 9.31 s (1H, NH), 12.29 s (1H, NH). Found, %: C 65.52; H 5.55; N 16.31; S 6.33. $C_{28}H_{28}N_6O_2S$. Calculated, %: C 65.60; H 5.51; N 16.39; S 6.26.

2-{[6-Cyano-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]-pyridin-3-yl]sulfanyl}-*N*-(1,3-thiazol-2-yl)acetamide (6r). Yield 0.73 g (72%), mp 254–256°C. IR spectrum, ν, cm^{-1}: 3377, 3329 (NH), 2210 (CN), 1672 (CO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 s (6H,

CH_3), 2.33 s (3H, CH_3), 2.62 s (2H, 7-H), 3.86 s (3H, OCH_3), 4.16 s (2H, SCH_2), 4.85 s (2H, 10-H), 6.81–6.89 m (4H, H_{arom}), 6.94–7.00 m (3H, H_{arom}), 8.07 d.d (1H, H_{arom}, J = 7.8, 1.1 Hz), 9.40 s (1H, NH), 9.63 s (1H, NH). Found, %: C 57.11; H 4.55; N 19.46; S 12.59. $C_{24}H_{23}N_7O_2S_2$. Calculated, %: C 57.01; H 4.59; N 19.39; S 12.68.

2-{[6-Cyano-8,8-dimethyl-5-(4-methylanilino)-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]-pyridin-3-yl]sulfanyl}-*N*-(2-methoxyphenyl)acetamide (6s). Yield 0.77 g (73%), mp 229–230°C. IR spectrum, ν, cm^{-1}: 3372, 3327 (NH), 2208 (CN), 1666 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 s (6H, CH_3), 2.35 s (3H, CH_3), 2.61 s (2H, 7-H), 3.98 s (2H, SCH_2), 4.28 d (2H, NHC**H**$_2$, J = 5.8 Hz), 4.85 s (2H, 10-H), 6.90–6.97 m (2H, H_{arom}), 7.06–7.27 m (7H, H_{arom}), 8.68 t (1H, NH, J = 5.8 Hz), 9.72 s (1H, NH). Found, %: C 63.54; H 5.37; N 15.83; S 6.12. $C_{28}H_{28}N_6O_3S$. Calculated, %: C 63.62; H 5.34; N 15.90; S 6.07.

8,8-Dimethyl-5-(2-methylanilino)-3-{[2-oxo-2-(pyrrolidin-1-yl)ethyl]sulfanyl}-7,10-dihydro-8*H*-pyrano[3,4-*c*][1,2,4]triazolo[4,3-*a*]pyridine-6-carbonitrile (6t). Yield 0.71 g (75%), mp 233–234°C. IR spectrum, ν, cm^{-1}: 3325 (NH), 2210 (CN), 1665 (CO). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 s (6H, CH_3), 1.78–1.87 m (2H, CH_2), 1.90–2.00 m (2H, CH_2), 2.36 s (3H, CH_3), 2.57 s (2H, 7-H), 3.35 t (2H, NCH_2, J = 7.8 Hz), 3.48 t (2H, NCH_2, J = 7.8 Hz), 4.15 s (2H, SCH_2), 4.83 s (2H, 10-H), 7.04–7.18 m (2H, H_{arom}), 7.19–7.24 m (2H, H_{arom}), 10.00 s (1H, NH). Found, %: C 62.93; H 5.95; N 17.71; S 6.64. $C_{25}H_{28}N_6O_2S$. Calculated, %: C 63.00; H 5.92; N 17.63; S 6.73.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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